IN THE UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF TEXAS
WACO DIVISION

RAVGEN, INC., Plaintiff, vs. LABORATORY CORPORATION OF AMERICA HOLDINGS, Defendant.	Civil Action No. 6:20-CV-00969-ADA JURY TRIAL DEMANDED

DEFENDANT LABCORP'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

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Defendant Laboratory Corporation of America Holdings ("Labcorp") respectfully submits this Responsive Claim Construction Brief.

I. INTRODUCTION

There are four claim terms presented for argument. Although proposing "plain and ordinary meaning" for all of the terms, Plaintiff Ravgen, Inc. ("Ravgen") completely ignores the plain English reading of the claims. Instead, Ravgen (1) re-writes the claims in order to delete expressed claim language to improperly broaden the claims; or (2) re-writes the claims in order to save non-sensical claims. Accordingly, Ravgen's proposals and arguments should be rejected.

II. DISPUTED TERMS FOR ARGUMENT

There are eight terms in dispute. For four terms in dispute, the parties have agreed to present briefing and argument. Labcorp's arguments are set forth below. For the remaining four, the parties agreed to forego briefing and rely on prior briefings and arguments from other cases[1] as set forth in § III below.

A. "free fetal DNA isolated" / "isolating free fetal nucleic acid" / "isolating free nucleic acid" ('277 Patent,[2] Claims 55, 81; '720 Patent,[3] Claim 1)

Ravgen's Proposal	Labcorp's Proposal
plain and ordinary meaning	"separate out free fetal DNA from everything else" / "separating out free fetal nucleic acid from everything else" / "separating out free nucleic acid from everything else"

The Court construed these claim terms as "plain and ordinary meaning" in *Natera* (at Dkt. 88). However, under the disguise of "plain and ordinary meaning," Ravgen improperly attempts to read out the word "fetal" expressly claimed in the '277 Patent. Ravgen argues that "the plain

[1] *Ravgen, Inc. v. Natera, Inc.*, No. 1:20-cv-00692-ADA (W.D. Tex.) ("*Natera*") and *Ravgen, Inc. v. PerkinElmer, Inc.*, No. 1:20-cv-00822-ADA (W.D. Tex.) ("*PerkinElmer*").

[2] U.S. Patent No. 7,332,277.

[3] U.S. Patent No. 7,727,720.

meaning of isolating nucleic acids encompasses well-known, standard techniques in the art to remove or reduce other components in a nucleic acid sample." Dkt. 48 (Opening Brief ("Op. Br.")) at 4. In doing so, Ravgen completely ignores the fundamental difference between the "isolating" terms found in the '277 Patent and the '720 Patent. The '277 Patent expressly limits the "isolating" to "free ***fetal*** DNA" or "free ***fetal*** nucleic acid." The '720 Patent, on the other hand, does not claim "fetal." Instead, the '720 Patent claims "isolating free nucleic acid." Accordingly, the "isolating" terms in both patents—one with "fetal," the other not—cannot have the same meaning or the same scope. But that is what Ravgen wants "plain and ordinary meaning" to be: re-writing the claim to delete the word "fetal."

The reason for Ravgen's improper insistence is simple: Ravgen wants all the "isolating" terms, whether it has "fetal" or not, to include ***maternal*** DNA. But this is inconsistent with the claim language and the specification (which describes, contrary to Ravgen's argument, isolating fetal DNA from everything else, including maternal DNA). Accordingly, Labcorp's construction should be adopted because it is consistent with the plain and ordinary meaning, the specification, and the prosecution history.[4]

1. Expressly Claimed Language "Fetal" in the '277 Patent Cannot Be Ignored

Claims 55 and 81 of the '277 Patent state as follows:

> **55.** A method comprising determining the sequence of a locus of interest on ***free fetal DNA isolated*** from a sample obtained from a pregnant female, . . .
>
> **81.** A method for preparing a sample for analysis comprising ***isolating free fetal nucleic acid*** from a the sample, . . .

[4] Because there is a dispute between the parties as to the scope of the claims and what a plain and ordinary meaning encompasses, this dispute should be resolved by the Court. *See, e.g.*, *O2 Micro Int'l, Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1362 (Fed. Cir. 2008) ("When the parties present a fundamental dispute regarding the scope of a claim term, it is the court's duty to resolve it."); *Eon Corp. IP Holdings v. Silver Spring Networks, Inc.*, 815 F.3d 1314, 1318 (Fed. Cir. 2016).

Dkt. 48-2 ('277 Patent) at 472:66-473:5, 474:52-57 (emphasis added).

Claim 1 of the '720 Patent states as follows:

> **1.** A method for detecting a free nucleic acid, wherein said method comprises: (a) ***isolating free nucleic acid*** from a non-cellular fraction of a sample, . . .

Dkt. 48-4 ('720 Patent) at 535:15-21 (emphasis added).

Because claim 1 of the '720 Patent does not limit the "isolating" to any specific type of free nucleic acid, the free nucleic acid being isolated can be fetal and/or maternal. There is no dispute there. But claims 55 and 81 of the '277 Patent are different: they expressly limit the isolating to free "***fetal***" DNA or nucleic acid. "It is axiomatic that '[c]laims, not the specification embodiments, define the scope of protection.'" *Dow Chem. Co. v. Sumitomo Chem. Co.,* 257 F.3d 1364, 1378 (Fed. Cir. 2001) (quoting *Am. Permahedge, Inc. v. Barcana, Inc.,* 105 F.3d 1441, 1444 (Fed. Cir. 1997)); *see also Renishaw PLC v. Societa' per Azioni,* 158 F.3d 1243, 1248 (Fed. Cir. 1998) ("[T]he claims define the scope of the right to exclude; the claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim.").

Indeed, Ravgen chose to limit claims 55 and 81 of the '277 Patent to isolating only the free "fetal" DNA or nucleic acid. In a May 30, 2007 response to a rejection based on prior art, Ravgen amended claim 58 (issued claim 55) by adding the word "isolated" to the term "free fetal DNA" to read "free fetal DNA <u>isolated</u>," thus changing the scope of the claim. Ex. C, 05/30/07 Amendment ('277 Patent File History) at RAVGEN-00013001. Similarly, Ravgen amended claim 87 (issued claim 81) by adding the word "fetal" to the term "free nucleic acid" to read "free <u>fetal</u> nucleic acid," similarly changing the scope of the claim. *Id.* at RAVGEN-00013005. Ravgen thus explicitly narrowed the scope of the terms to recite only ***<u>fetal</u>*** nucleic acid or DNA and isolating such fetal nucleic acid or DNA. Ravgen's proposed construction would wholly ignore these claim amendments, which it used to secure allowance.

Even more troubling to Ravgen's proposed construction is the fact that Ravgen told the Patent Office the exact opposite thing it is telling this Court. During prosecution, Ravgen described an earlier versions of claim 58 (reciting free ***fetal*** DNA) and claim 87 (at which point in time only recited free nucleic acids) as having a different scope. More particularly, in an Interview Summary, the Examiner described claims 58 and 87 by stating that " Claims 58 [issued claim 55], 87 [issued claim 81] and 152 was [*sic*] directed towards the isolation and analyse [*sic*] free fetal DNA [i.e. extracellular DNA derived from the fetus and present in a sample taken from a pregnant females [*sic*] (e.g. blood)]." Ex. D, 10/12/06 Office Action ('277 File History) at RAVGEN-00012835. In response to that description, Ravgen corrected the Patent Office and stated that the term "free nucleic acid" in claim 87 encompassed both fetal and maternal DNA: "the nucleic acid isolated in the method of claim 87 encompasses, but is not necessarily limited to, either fetal DNA or nucleic acid present in a sample taken from a pregnant female." Ex. E, 12/12/06 Amendment ('277 File History) at RAVGEN-00012875. But Ravgen did not similarly characterize then pending claim 58, which again recited "free ***fetal*** DNA," in that way. *See id.* By not including claim 58 in Ravgen's "correction" of the Patent Office's statement, Ravgen both admitted that the Patent Office's interpretation of then pending claim 58 was correct, and reinforced that the term's plain and ordinary meaning at the time referred only to ***fetal*** DNA. Simply put: Ravgen's position here is contradicted by what it told the Patent Office to secure allowance of the claims.

Other claims of the Patents-in-Suit also support Labcorp's position. For example, unasserted independent claims 1 and 116 of the '277 Patent provide further evidence that the term "fetal" should be given meaning. Claims 1 and 116 recite "template DNA," which is expressly claimed as including a "***mixture*** of maternal DNA and fetal DNA." Dkt. 48-2 ('277 Patent) at 469:13-15, 477:4-6 (emphasis added). Similarly, claim 1 of the '720 Patent simply recites "nucleic

acid." Dkt. 48-4 ('720 Patent) 535:15-21. Unlike claims 1 and 116 of the '277 Patent and claim 1 of the '720 Patent, claims 55 and 81 specifically recite "***fetal***" DNA or nucleic acids. If Ravgen wanted claims 55 and 81 to have the same scope as these other claims, Ravgen could have chosen not to expressly put such a limitation in the claims, just like it did for claims 1 and 116 of the '277 Patent and claim 1 of the '720 Patent.

Therefore, the terms including "fetal" and not including "fetal" must have different meaning. *See, e.g.*, *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.,* 381 F.3d 1111, 1119 (Fed. Cir. 2004) (reversing the district court's construction of the term "operatively connected" because it largely "reads the term 'operatively' out of the phrase 'operatively connected'"); *id.* ("While not an absolute rule, all claim terms are presumed to have meaning in a claim."); *Karlin Tech. Inc. v. Surgical Dynamics, Inc.,* 177 F.3d 968, 971-72 (Fed. Cir. 1999) ("[T]he common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope."); *Seachange Int'l Inc. v. C-COR, Inc.,* 413 F.3d 1361, 1369 (Fed. Cir. 2005) ("[T]here is still a presumption that two independent claims have different scope when different words or phrases are used in those claims."). Ravgen's position ignores the difference in scope between these terms and is an attempt to broaden the isolating fetal claim terms in a blatant attempt to re-write the claims.

2. The Specification Describes Isolating Only the Fetal DNA

Ravgen argues that Labcorp's proposal should not be accepted because the specification does not describe isolating only the free fetal nucleic acid, which does not include the free maternal nucleic acid. *See, e.g.*, Op. Br. at 6 ("None of these isolation techniques result in the isolation of cell-free fetal nucleic acid from everything else, including cell-free maternal nucleic acids."); *id.* at 5 ("But these proposed constructions are incorrect because they import an additional limitation into the plain language and because they would exclude every example provided in the

specification."). But Ravgen ignores that the Patents-in-Suit describe at least two different embodiments—one isolating "free nucleic acid," and the other, isolating "free ***fetal*** nucleic acid":

> ***In an embodiment***, the present invention provides a ***method for isolating nucleic acid*** said method comprising (a) obtaining a sample containing nucleic acid; (b) adding a cell lysis inhibitor, cell membrane stabilizer, or cross-linker to the sample of (a); and (c) isolating nucleic acid. In an embodiment, the method is used for ***isolating free nucleic acid***. In an embodiment, the method is used for ***isolating free fetal nucleic acid***. ***In another embodiment***, the present invention provides a ***method for isolating free fetal nucleic acid*** said method comprising (a) obtaining a sample containing nucleic acid; (b) adding a cell lysis inhibitor, cell membrane stabilizer, or cross-linker to the sample of (a); (c) isolating the plasma from the blood sample, wherein the plasma is isolated by centrifuging the blood sample; and (d) removing the supernatant, which contains the plasma, using procedures to minimize disruption of the "buffy-coat."

Dkt. 48-1 ('277 Patent) at 15:22-38 (emphasis added); *also compare id.* at 26:35-39 ("In another embodiment, the present invention is directed to a method for ***isolating free DNA*** . . .") (emphasis added) with *id.* at 26:40-44 ("In another embodiment, the present invention is directed to a method for ***isolating free fetal DNA*** . . .") (emphasis added); *see also, e.g.*, Dkt. 48-3 ('720 Patent) at 11:9-25.

As shown above, the specification describes two different methods in two different embodiments for (1) isolating "free nucleic acid" and (2) isolating "free ***fetal*** nucleic acid." Accordingly, like the claimed language in the '277 and '720 Patents, the specification also provides that isolating "free nucleic acid" and isolating "free ***fetal*** nucleic acid" must be different. The word "fetal" must have meaning.

Indeed, the portions of specification upon which Ravgen relies are not inconsistent with Labcorp's proposal. Ravgen relies on '277 Patent at 31:48-51 (Op. Br. at 4), but when read in full context, this part of the specification goes to isolating both the fetal ***and*** maternal nucleic acid together, which is ***not*** what is claimed in claims 55 and 81 of the '277 Patent:

> In another embodiment, the template DNA contains ***both maternal DNA and fetal DNA***. In a preferred embodiment, template DNA is obtained from blood of a

> pregnant female. . . .
>
> The blood sample is centrifuged to separate the plasma from the maternal cells. The plasma and maternal cell fractions are transferred to separate tubes and re-centrifuged. The plasma fraction contains ***cell-free fetal DNA and maternal DNA***. Any standard DNA isolation technique can be used to ***isolate the fetal DNA and the maternal DNA*** including but not limited to QIAamp DNA Blood Midi Kit supplied by QIAGEN (Catalog number 51183).

Dkt. 48-1 ('277 Patent) at 31:32-51 (emphasis added); *see also* Dkt. 48-3 ('720 Patent) at 32:41-60 (same). Ravgen also relies on part of Example 4 in the '277 Patent at 89:17-34 (Op. Br. at 6). Again, this portion of the specification goes to the embodiment of isolating just the DNA (e.g., both fetal and maternal), not the other embodiment of isolating only the ***fetal*** DNA. *See* Dkt. 48-1 ('277 Patent) at 89:17-37 and Dkt. 48-3 ('720 Patent) at 89:40-57 ("Preparation of Template DNA" in Example 4).

Ravgen also claims that Labcorp's proposed construction would exclude "every example" of the specification. Op. Br. at 6. This is false. Ravgen ignores that the specification specifically provides numerous embodiments and examples purporting to demonstrate complete isolation of fetal DNA. For example, Example 15 describes techniques where 10 samples (out of a total of 69 samples) ***completely*** isolated fetal DNA. Table XXI presents data (excerpts below) from the techniques of Example 15 that show ***100% Fetal DNA*** isolated from samples:

TABLE XXI

Formalin increases the percentage of free fetal DNA in blood samples collected at numerous clinical sites from women at various stages of gestation.

Sample	Wks Gestation	Fetal Genomes/ml	% Fetal DNA
1	16	80	25
2	19	1066	>50
3	17	52	50
4	22	166	25
5	32	457	50
6	19	400	100
7	18	800	100
8	17	100	50
9	16	50	25
10	17	25	12.5
11	16	94.74	12.5
12	16	34.60	50
13	16	22.5	25
14	17	50	12.5
15	17	26.48	12.5
16	17	45.00	25
17	17	94.7	100
18	17	28.13	6.25
19	19	28.13	25
20	20	11.25	12.5
21	15	11.25	12.5
22	11	16.66	12.5
23	18	13.23	25
24	18	12.50	6.25
25	16	112.50	100
26	17	124.13	25
27	14	90.00	50
28	11	100.00	100
29	18	232.00	100
30	19	626.00	100
31	19	112.50	100
32	16	423.50	100
33	16	423.50	25
34	11	105.88	25
35	16	49.60	3.1
36	11	11.84	12.5
37	16	120.00	25
38	18	342.90	100
39	17	51.43	25
40	18	225.00	6.25
41	17	400.00	12.5
42	28	180.00	25
43	17	20.45	12.5
44	18	25.73	25
45	16	68.68	3.1
46	17	218.18	25
47	15	75.00	6.25
48	16	40.58	3.1
49	17	100.00	25
50	17	14.06	12.5
51	22	22.50	12.5
52	15	28.13	12.5
53	17	50.00	3.125
54	18	58.00	50

TABLE XXI-continued

Formalin increases the percentage of free fetal DNA in blood samples collected at numerous clinical sites from women at various stages of gestation.

Sample	Wks Gestation	Fetal Genomes/ml	% Fetal DNA
55	14	100.00	25
56	16	58.08	25
57	16	13.64	12.5
58	16	25.00	6.25
59	20	45.00	25
60	16	23.69	12.5
61	18	5.92	6.25
62	15	28.13	6.25
63	17	50.00	25
63			
64	16	360.00	50
65	16	25.00	12.5
66	16	48.65	25

TABLE XXI-continued

Formalin increases the percentage of free fetal DNA in blood samples collected at numerous clinical sites from women at various stages of gestation.

Sample	Wks Gestation	Fetal Genomes/ml	% Fetal DNA
67	16	47.38	12.5
68	14	26.45	50
69	17	124.15	25
Average	17	131.15	33.6

Dkt. 48-2 ('277 Patent) at 224:15-226:15 (highlights added).

Further, Ravgen's reliance on *Oatey Co. v. IPS Corp.*, 514 F.3d 1271 (Fed. Cir. 2008) (Op. Br. at 5-6) is misplaced. *Oatey* involved construing a claim that excluded relevant embodiment as set forth in the claim. *Id.* at 1276 ("the structure in Figure 3 [which was excluded by the district court] is an embodiment of the invention as set forth in the specification and in claim 1."). That is not the case here. As discussed above, there are at least two different embodiments described in the patents. The terms in the '277 Patent with "fetal" go to the embodiment isolating only the

"fetal" DNA; the term in the '720 Patent (and other claims in the '277 Patent) without "fetal" go to the embodiment isolating generic free DNA. Therefore, there is no improper exclusion of relevant embodiments.

Even if Ravgen were correct that Labcorp's proposal excludes a relevant embodiment (which it does not), the Federal Circuit made clear that an embodiment does not trump expressed claim language. For example, in *Schoenhaus v. Genesco, Inc.,* 440 F.3d 1354 (Fed. Cir. 2006), the Federal Circuit rejected patentee's argument that because the preferred embodiment describes a "semi-rigid" material, the claim's usage of the word "rigid" should be construed to mean "semi-rigid." The Federal Circuit found that the "patentee's usage of the phrase 'semi-rigid material' in the specification, when referring to the material to be used in the manufacture of the orthotic device generally, is insufficient to disclaim the requirement in claim 1 that the material used to construct the 'heel seat' be 'rigid.'" *Id.* at 1358. The Federal Circuit also noted that "the specification language cited by plaintiffs was insufficient to 'clearly set forth a different definition' from the conventional usage of 'rigid' by ordinary practitioners in the field" and refused to depart from the conventional definition of "rigid" for claim construction. *Id.*; *see also id.* at 1359 ("where a patent specification includes a description lacking a feature, but the claim recites that feature, ***the language of the claim controls***.") (citing *Unique Concepts, Inc. v. Brown,* 939 F.2d 1558, 1562 (Fed. Cir. 1991)) (emphasis added).

3. Labcorp's Proposal is Consistent With the Plain and Ordinary Meaning and the Specification

Ravgen argues that Labcorp is rewriting the claim language by adding in a new requirement. Op. Br. at 5. Not so. Because the parties do not agree as to what "isolate" means in context of the proposed terms in the '277 and '720 Patents as discussed above, Labcorp's proposal (e.g., "separate out free fetal DNA from everything else") is consistent with the plain and ordinary

meaning. The plain and ordinary meaning of "isolate" means "to set apart from others : cause to be detached from others and alone." Ex. F, Webster's Third New International Dictionary, p. 1199 (2002) (LCRAV00009759-761). This meaning is consistent with how the term is used in biochemistry and molecular biology context: "to separate (a pure substance, a cell type, or a sample of a subcellular component) from a mixture or from naturally occurring material and then (usually) to characterize it; to separate and put into pure culture (a particular species or strain of a microorganism) from a mixture, sample, or biological specimen." Ex. G, Oxford Dictionary of Biochemistry and Molecular Biology, p. 346 (Revised ed. 2001) (LC-RAV00009756-758).

And Labcorp's proposed construction is consistent with how Ravgen used the term "isolate" throughout the specification in a variety of contexts. For example, the specification explains that nucleic acids can be "extracted, purified or isolated" for analysis—equating purification and isolation, both of which just mean separating the thing of interest from everything else. *See, e.g.*, Dkt. 48-1 ('277 Patent) at 34:12-14; *id.* at 89:29-31 (disclosing kit for "isolating" DNA as "for purification of DNA from blood cells"). Indeed, the specification consistently uses the term "isolating" as meaning separating from everything else when it discloses that one can isolate fetal DNA by isolating fetal cells from a variety of sources, including blood. *Id.* at 33:23-52. As the specification explains, the fetal cells are separated from everything else, including maternal cells, by using antibodies to "purify the fetal cells from the maternal serum." *Id.* The specification also describes separating certain types of DNA from other types of DNA. *Id.* at 82:36-39 (PCR products separated from genomic template DNA). It further describes isolating nucleic acids from non-nucleic acid materials that may be in the original sample. *Id.* at 34:29-32.

Thus, the patent specification consistently and regularly uses the term isolating to mean separating the thing of interest from everything else. And it uses the same term consistently in a

variety of contexts, including isolating fetal cells from non-fetal cells, isolating types of DNA from other types of DNA, and isolating nucleic acids from non-nucleic acid materials. Ravgen's attempt to remove any meaning from the terms "isolating" and "fetal," and to broaden the claim term to mean the same thing as claim terms not reciting fetal, invites error and is not a "plain and ordinary" meaning.

Finally, even if the Court decides not to adopt Labcorp's proposal, at the very least, for the reasons discussed above, the terms that contain the word "fetal" cannot mean the same thing as the terms that do not contain the word "fetal." Accordingly, for the terms "free ***fetal*** DNA isolated" and "isolating free ***fetal*** nucleic acid" claimed in the '277 Patent, it should be made clear that virtually no ***maternal*** DNA or ***maternal*** nucleic acid is isolated with the ***fetal*** DNA or ***fetal*** nucleic acid.

B. "free . . . DNA" / "free . . . nucleic acid" ('277 Patent, Claims 55, 58, 81, 130; '720 Patent, Claims 1, 21)

Ravgen's Proposal	Labcorp's Proposal
plain and ordinary meaning	"extracellular, i.e., outside the cell . . . DNA" / "extracellular, i.e., outside the cell . . . nucleic acid"

It does not appear that Ravgen disputes that the plain and ordinary meaning of the term "free," used in context of DNA or nucleic acid, means "extracellular," which in plain language means "outside the cell." In fact, Ravgen's own expert, Dr. Brian Van Ness uses these terms interchangeably in his declaration. Dkt. 48-7 (Van Ness Decl.) at ¶ 21 ("The vast majority of human DNA in blood is contained within the cells; however, ***some DNA may be found circulating outside of the cells in plasma and is considered extracellular, cell-free, or free***.") (emphasis added). Further, Ravgen does not argue that Labcorp's proposal is wrong in any way. *See* Op. Br. at 2-3. Accordingly, Ravgen should confirm now whether it agrees that the plain and ordinary

meaning of the term "free" DNA or nucleotide means "extracellular, i.e., outside the cell." If it does not agree, it should provide why Ravgen disputes the meaning. If it agrees, Ravgen should be prevented from arguing later that the term "free" DNA or nucleotide means something other than "extracellular, i.e., outside the cell."

C. "said sample" ('277 Patent, Claims 85, 88; '720 Patent, Claims 5, 6)

Ravgen's Proposal	Labcorp's Proposal
plain and ordinary meaning	Indefinite

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.,* 572 U.S. 898, 901 (2014). Here, "said sample" as used in claim 88 of the '277 Patent and claim 6 of the '720 Patent requires "***said [blood] is obtained from plasma from said blood***," which is unreasonably circular and inherently unclear. Further, claim 85 of the '277 Patent and claim 5 of the '720 Patent are non-sensical and impossible because the claims they depend on fail to identify any appropriate source from which the claimed blood can be obtained. Thus, a person of ordinary skill in the art ("POSITA") cannot, with reasonable certainly, determine the scope of these claims.[5]

1. Claim Language

Claims 85 and 88 of the '277 Patent ultimately depend back to claim 81 as follows:

> **81.** A method for preparing ***a sample*** for analysis comprising isolating free fetal nucleic acid from ***the sample***, wherein ***said sample*** comprises an agent . . .

[5] Ravgen complains that Labcorp was able to apply a plain and ordinary meaning of this term in the *inter partes* review proceedings. Op. Br. at 11. But "[i]nter partes review cannot replace the district court in all instances, for example, when claims are challenged in district court as invalid based . . . on grounds of indefiniteness." *Synopsys, Inc. v. Mentor Graphics Corp.,* 814 F.3d 1309, 1316 (Fed. Cir. 2016) *overruled on other grounds by Aqua Prods., Inc. v. Matal,* 872 F.3d 1290 (Fed. Cir. 2017). Nor did Labcorp have the option of challenging indefiniteness in the *inter partes* review proceeding. *See* 35 U.S.C. § 311(b); *see also Samsung Elecs. Am., Inc. v. Prisua Eng'g Corp.*, 948 F.3d 1342 (Fed. Cir. 2020).

> **84.** The method of claim 81, wherein ***the sample is obtained from a source selected from the group consisting of blood***, serum, plasma, saliva, urine, tear, vaginal secretion, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascitic fluid, fecal matter, and body exudates.
>
> **85.** The method of claim 84, wherein ***said sample is blood***.
>
> **86.** The method of claim 85, wherein ***said blood*** is from a pregnant female.
>
> **87.** The method of claim 86, wherein ***said blood*** is obtained from a human pregnant female when the fetus is at a gestational age selected from the group consisting of: 0-4, 4-8, 8-12, 12-16, 16-20, 20-24, 24-28, 28-32, 32-36, 36-40, 40-44, 44-48, 48-52, and more than 52 weeks.
>
> **88.** The method of claim 87, wherein ***said sample is obtained from plasma from said blood***.

Dkt. 48-2 ('277 Patent) at 474:52-475:12 (emphasis added).

Similar language is found in claims 5 and 6 of the '720 Patent, which ultimately depend back to claim 1:

> **1**. A method for detecting a free nucleic acid, wherein said method comprises: (a) isolating free nucleic acid from a non-cellular fraction of ***a sample***, wherein ***said sample*** comprises an agent . . .
>
> **4.** The method of claim 1, wherein ***the sample is obtained from a source selected from the group consisting of***: tissue, ***blood***, serum, plasma, saliva, urine, tear, vaginal secretion, umbilical cord blood, chorionic villi, amniotic fluid, embryonic tissue, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascitic fluid, fecal matter, and body exudates.
>
> **5.** The method of claim 4, wherein ***said sample is blood***.
>
> **6.** The method of claim 5, wherein ***said sample is obtained from plasma from said blood***.

Dkt. 48-4 ('720 Patent) at 535:15-39 (emphasis added).

2. "Said Sample" in Claim 88 of the '277 Patent and Claim 6 of the '720 Patent is Non-Sensical

Claim 85 of the '277 Patent states that "said sample ***is*** blood." Dkt. 42-8 ('277 Patent) at 475:3 (emphasis added). Claims 86 and 87, which depend on claim 85, then identifies where that

blood is from. But claim 88 refers to the "sample" again, but this time, it claims that the "sample is obtained from plasma" from the blood that was referred to in previous claims. And, claim 88 depends back to claim 85, which had already defined the "sample" as "blood." So, claim 88, replacing "sample" to "blood," reads as follows: ***said [blood] is obtained from plasma from said blood***. This is nonsensical and impossible. Ex. A, Fletcher Decl. at ¶¶ 25-26. Blood cannot be obtained from plasma, because plasma is a component of blood. Indeed, the rest of the claim states that plasma is obtained from blood, making the whole claim unreasonably circular and inherently unclear. *Id.*

Claim 6 of the '720 Patent has the exact same problem as claim 88 of the '277 Patent. Claim 6 depends on claim 5, which defines "said sample" as "blood." Therefore, replacing "said sample" with "blood," claim 6 reads as follows: ***said [blood] is obtained from plasma from said blood***. This, like claim 88 of the '277 Patent, is non-sensical, impossible, unreasonably circular, and inherently unclear. *Id.* at ¶¶ 27-28.

3. "Said Sample" in Claim 85 of the '277 Patent and Claim 5 of the '720 Patent is Also Non-Sensical

The "said sample" claimed in claim 85 of the '277 Patent and claim 5 of the '720 Patent is also non-sensical for a different reason. Claim 85 depends on claim 84, which expressly lists ***sources*** from which "the sample" can be obtained. Dkt. 48-2 ('277 Patent) at 474:65-475:2. But claim 85 states that "***said sample is blood***." *Id.* at 475:3. And blood cannot be ***obtained*** from any of the sources listed in claim 84, which claim 85 depends on.

First, it does not make sense to obtain blood from blood (which is one of the listed sources). Ex. A, Fletcher Decl. at ¶ 31. This is unreasonably circular and does not make any sense. *Id.* Second, blood cannot be obtained from the rest of the listed sources: "serum, plasma, saliva, urine, tear, vaginal secretion, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascitic

fluid, fecal matter, and body exudates." *Id.* For example, serum and plasma are components of blood, so it cannot be a source from which blood can be obtained. *Id.* And blood cannot be obtained from other specific fluids (e.g., urine) and matters (e.g., fecal matter) identified. *Id.* Accordingly, because "said sample" as claimed in claim 85 is "blood," and blood cannot be obtained from any of the sources listed in claim 84, which claim 85 depends on, claim 85 is nonsensical and impossible. *Id.* at ¶ 32.

Claim 5 of the '720 Patent has the identical language to claim 85 of the '277 Patent. Claim 5 depends on claim 4, which identifies a list of sources from which the sample is obtained. Dkt. 48-4 ('720 Patent) at 535:30-36. The source listed in claim 4 is the same as claim 84 of the '277 Patent, except it also adds "umbilical cord blood, chorionic villi, amniotic fluid, [and] embryonic tissue." Similar to the other liquids and matters listed, none of these can be a source of blood. Ex. A, Fletcher Decl. at ¶ 33. For example, umbilical cord blood is blood from umbilical cord, and as discussed above, it does not make sense that blood is obtained from blood. *Id.* Also, blood cannot be obtained from chorionic villi, amniotic fluid, or embryonic tissue. *Id.* Accordingly, like claim 85 of the '277 Patent, because "said sample" as claimed in claim 5 is "blood," and blood cannot be obtained from any of the sources listed in claim 4, which claim 5 depends on, claim 5 is nonsensical and impossible. *Id.* at ¶ 34.

4. Ravgen Ignores the Expressed Claim Language

In arguing that a POSITA would understand that the sample in question is obtained from plasma portion of the blood, Ravgen completely ignores the expressed claim language. Op. Br. at 12-14. There is no dispute that plasma is a component of blood. Op. Br. at 12 ("plasma, the liquid portion of unclotted blood in which cells may be suspended."); Ex. A, Fletcher Decl. at ¶ 26. But Ravgen goes one step further, arguing that plasma ***is*** blood. *See, e.g.*, *id.* at 13 ("Labcorp's theory appears to be based on the incorrect notion that plasma is not blood."). This is akin to agreeing

that one component of ranch dressing is buttermilk, but unreasonably going one step further to say that, therefore, buttermilk ***is*** ranch dressing. Plasma is a component of blood; it is ***not*** blood. Ex. A, Fletcher Decl. at ¶ 26.

Even if Ravgen is correct that plasma is blood (it is not), "said sample" as used in the claims in question still would not make sense. Claim 88 of the '277 Patent and claim 6 of the '720 Patent would now read: ***said [plasma] is obtained from plasma from said blood***. Actually, this would be even worse: it is more non-sensical and more unreasonably circular. If Ravgen wanted to claim that a sample is plasma, then Ravgen could have easily written a claim to state that "said sample is plasma." Ravgen did not do so, and it cannot now expect the public to re-write and understand its non-sensical, poorly written claims.

5. Non-Sensical Claims Are Indefinite

Non-sensical claims are indefinite. *See, e.g.*, *Trs. of Columbia Univ. in City of New York v. Symantec Corp.,* 811 F.3d 1359, 1367 (Fed. Cir. 2016) ("the claims describe the step of extracting machine code instructions from something that does not have machine code instructions . . . [and thus] [t]he claims are nonsensical in the way a claim of extracting orange juice from apples would be, and are thus indefinite."); *Zeta Glob. Corp. v. Maropost Marketing Cloud Inc.,* No. 20 Civ. 3951(LGS), 2021 WL 2823563, at *5 (S.D.N.Y. July 7, 2021) ("When properly read as incorporating Claim 1, Claim 6 thus claims a failure message (1) received by the sender when the ISP is *unable* to deliver an email to the recipient (2) *and* is created only *after* the email is delivered to the recipient. This combined claim language is contradictory and nonsensical, and no POSITA reading the '439 Patent would understand the term 'failure message' as limited by when it is received – that is, simultaneously after delivery and upon non-delivery.") (emphasis in original); *Image Processing Techs., LLC v. Samsung Elec. Co.,* Case No. 2:16-cv-505, 2017 WL 2672616, at *15-16 (E.D. Tex. June 21, 2017) (finding that "a classification unit coupled to the

input portion and the histogram unit, and configured to determine the data in the history that satisfy a selected criterion" to be indefinite because it was non-sensical as written since the classification unit cannot evaluate data in the histogram because another limitation requires the calculation results of this claim to create the histogram); *Omni MedSci, Inc. v. Apple Inc.,* No. 2:18-cv-00429-RWS, 2019 WL 3818762, at *13 (E.D. Tex. Aug. 14, 2019) (finding "wherein the modulation frequency has a phase" to be indefinite because the claims as written were nonsensical because a modulation frequency cannot have a phase); *Koki Holdings Co. v. Kyocera Senco Indus. Tools, Inc.,* No. 18-313-CFC, 2021 WL 1092579, at *1-2 (D. Del. Mar. 22, 2021) (finding indefiniteness for a claim that required "a trigger valve exterior frame to which the main valve control channel is fluidly connected," which is physically impossible because the "trigger valve exterior frame is indisputably a solid" and a solid cannot be a fluid).

Just like these cases, "said sample" as used in claims 85 and 88 of the '277 Patent and claims 5 and 6 of the '720 Patent, is non-sensical, inherently unclear, impossible, and fails to inform a POSITA, with reasonable certainly, the scope of these claims. Accordingly, these claims are indefinite.

D. "method for preparing a sample for analysis comprising isolating free fetal nucleic acid from the sample" ('277 Patent, Claim 81)

Ravgen's Proposal	Labcorp's Proposal
plain and ordinary meaning	Indefinite

Claim 81 of the '277 Patent states:

> **81.** A ***method for preparing a sample for analysis comprising isolating free fetal nucleic acid from the sample***, wherein said sample comprises an agent . . .

Dkt. 48-2 ('277 Patent) at 474:52-54 (emphasis added). It is clear from the plain language of the claim that claim 81 is directed to a "***method for preparing a sample for analysis***," i.e., the sample as identified here is the thing that is going to be analyzed. Next, the preparation method comprises

of "***isolating free fetal nucleic acid from the sample***," i.e., the free fetal nucleic acid is isolated ***from*** the sample that is going to be analyzed. In other words, the sample that is to be analyzed should no longer have free fetal nucleic acid, as the fetal nucleic acid is isolated ***from*** it. Ex. A, Fletcher Decl. at ¶ 36.

But this plain English reading of the claim does not make any sense to a POSITA in light of the specification. *Id.* at ¶¶ 35-41. The Field of the Invention of the '277 Patent states that: "The present invention provides a rapid non-invasive method for determining the sequence of DNA from a fetus." Dkt. 48-1 ('277 Patent) at 1:33-35. Thus, a POSITA would understand the purpose of the isolation of fetal DNA is so that the fetal DNA can be analyzed. Indeed, Ravgen admits that "the portion of the sample that is to be analyzed is the free nucleic acid." Op. Br. at 9. But the express language of claim 81 does the opposite: it separates out the fetal nucleic acid from the sample that is to be analyzed. Ex. A, Fletcher Decl. at ¶¶ 35-41. This is non-sensical; therefore, indefinite. *Id.*; *see* § II.C.5 above (citing *Trs. of Columbia Univ.,* 811 F.3d at 1367; *Zeta Global Corp.*, 2021 WL 2823563 at *5; *Image Processing Techs.,* 2017 WL 2672616 at *15-16; *Omni MedSci, Inc.*, 2019 WL 3818762 at *13; *Koki Holdings Co.,* 2021 WL 1092579 at *1-2).

Ravgen's "plain and ordinary meaning" of claim 81 completely ignores the expressed language of the claim. Ravgen argues that "[i]n context of preparing samples containing nucleic acids, that preparation often involves separating or removing certain components of the sample so that ***the components of interest (e.g., the nucleic acids) can be analyzed more easily***." Op. Br. at 9 (emphasis added). But in claim 81, the "component of interest" (i.e., "free fetal nucleic acid") is separated out ***from*** the sample to be analyzed, rather than containing the component of interest. Ex. A, Fletcher Decl. at ¶¶ 35-41.

In order to save this non-sensical claim, Ravgen introduces a new concept not expressed in

the claim—"the ***original*** sample"—by arguing that "a POSITA would prepare ***the original sample*** for analysis by isolating some components of the sample." Op. Br. at 9; *see also id.* at 9-10 ("In [Example 15 of the '277 Patent], the blood example is being prepared for analysis by isolating the DNA component of that blood sample."). In other words, Ravgen is describing having two different samples: (1) the "original sample" (i.e., blood), which is the starting point; and (2) the "resulting sample" (i.e., free DNA component) that is to be analyzed. *See* Ex. A, Fletcher Decl. at ¶¶ 38-40. But this is not what the claim says and is inconsistent with the plain and ordinary meaning of the claim.[6] Indeed, to support the "plain and ordinary" meaning, Ravgen must rewrite the claim as:

> method for preparing a **resulting** sample for analysis comprising isolating free fetal nucleic acid from ~~the~~ **an original** sample

This is improper. *See, e.g.*, *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) ("This court, however, repeatedly and consistently has recognized that courts may not redraft claims, whether to make them operable or to sustain their validity.").

Even if the Court does not find claim 81 of the '277 Patent indefinite, at the very least, Labcorp respectfully submits that the "plain and ordinary" meaning of the term "method for preparing a sample for analysis comprising isolating free fetal nucleic acid from the sample" cannot include preparing a sample for analysis where that sample contains free fetal nucleic acid. This is because the plain and ordinary reading the term requires isolating or separating out the free fetal nucleic acid ***from*** the sample to be analyzed.

III. DISPUTED TERMS ADOPTING ARGUMENTS AND EVIDENCE FROM OTHER CASES

The Court has already construed the following terms in *Natera* at Dkt. 88 (*see also* Dkt.

[6] Contrary to Ravgen's argument, Labcorp is not arguing that the "method for preparing a sample for analysis" requires "a performance of analysis of any sample." Op. Br. at 10.

93) and *PerkinElmer* at Dkt. 78. The parties agreed to forego briefing on these terms and rely on prior briefings and arguments from *Natera* and/or *PerkinElmer*. Labcorp's proposal is set forth below:[7]

1. "determining the sequence of a locus of interest" ('277 Patent, Claim 55): "determining the identity of one nucleotide or of contiguous nucleotides or nucleosides of a selected region of nucleic acid." *See, e.g.*, *PerkinElmer* at Dkts. 50, 55, 62, and February 9, 2021 *Markman* hearing.

2. "agent that [inhibits cell lysis to inhibit the lysis of cells/inhibits lysis of cells/impedes cell lysis] . . . wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor" / "said sample comprises an agent that [impedes cell lysis/inhibits lysis of cells], if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor" ('277 Patent, Claims 55, 81; '720 Patent, Claim 1): indefinite. *See, e.g.*, *PerkinElmer* at Dkts. 50, 55, 62 and February 9, 2021 *Markman* hearing; *Natera* at Dkts. 49, 57, 62, 63 and February 9, 2021 *Markman* hearing.

3. "formalin" ('277 Patent, Claims 60, 90-93, 132, 133): "a stock solution of formaldehyde, usually 37% weight to volume." *See, e.g.*, *PerkinElmer* at Dkts. 50, 55, 62, and February 9, 2021 *Markman* hearing.

4. "non-cellular fraction" ('720 Patent, Claim 1): "a separated portion substantially free of intact cells." *See, e.g.*, *PerkinElmer* at Dkts. 50, 55, 62 and February 9, 2021 *Markman* hearing.[8]

IV. CONCLUSION

For the foregoing reasons, Labcorp respectfully submits that its proposed constructions be adopted.

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[7] Labcorp reserves the right to challenge and/or appeal the Court's prior constructions in *Natera* and *PerkinElmer* Cases, to the extent adopted in this case, of all disputed terms between the parties in this action.

[8] Labcorp additionally relies on the following extrinsic evidence, which support this point: (1) *Fraction,* Oxford Dictionary of Biochemistry and Molecular Biology, p. 244 (Revised ed. 2001) ("any one of several portions of a mixture that can be separated by a fractional process, e.g. by fractional distillation or chromatography, and consisting either of a mixture or of a pure compound") (LCRAV00009780-782) (Ex. H); and Alberts et al., *Fractionation of Cells,* Molecular Biology of the Cell (4th ed. 2002) (https://www.ncbi.nlm.nih.gov/books/NBK26936/) (LC-RAV00009783-793) (Ex. I).

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CERTIFICATE OF SERVICE

I hereby certify that, on August 11, 2021 all counsel of record who are deemed to have consented to electronic service are being served with a copy of the foregoing document via the Court's CM/ECF system.

/s/ Aden M. Allen
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